EXHIBIT B

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF WEST VIRGINIA
CHARLESTON DIVISION

IN RE: ETHICON, INC., PELVIC REPAIR SYSTEM PRODUCTS LIABILITY LITIGATION	**Master File No. 2:12-MD-02327** **MDL 2327** **JOSEPH R. GOODWIN** **U.S. DISTRICT JUDGE**
THIS DOCUMENT RELATES TO: *Wave 5 Cases*	

EXPERT REPORT OF MARSHALL SHOEMAKER, M.D.
GYNEMESH PS, PROLIFT, PROLIFT+M, AND PROSIMA

I. INTRODUCTION

A. This report contains my opinions regarding the design, safety, and efficacy of the Gynecare Prolift Pelvic Floor Repair System, Gynecare PS Transvaginal Mesh, Prolift+M, and Prosima. It is my opinion that all these products were safe and effective and provided adequate warnings and instructions to doctors. This report will also contain a summary of my qualifications, training, education, and experience from which I base my opinions. I have reviewed and considered published medical literature and literature reviews, journal articles, textbooks, and materials provided to me by Counsel for Ethicon and Johnson & Johnson (including company documents, reports and depositions of plaintiff experts, discussed therein). I also have materials which I have reviewed as a preceptor for Gynecare throughout the years. The materials that support these opinions will be in my reference list. I do hold that these opinions are within a reasonable degree of medical certainty, and if I receive additional information prior to trial, I reserve the right to add or change my opinions.

B. I am currently being paid $500 an hour to prepare a written report and review materials and $700 an hour for depositions.

II. BACKGROUND.

A. My name is Marshall D. Shoemaker, MD. I attended the University of Alabama and graduated with a Bachelor of Science in Biology in 1979. I am Board Certified in Obstetrics and Gynecology and attended Texas Tech School of Medicine from 1979 to 1983. I did my residency at Parkland Memorial Hospital with The University of Texas Southwestern Medical School in Dallas from 1983 to 1987. I was chief resident in my fourth year of residency and was voted “Outstanding Resident” for 1987 by my peers. I joined a group of Parkland residents in a private practice in Corpus Christi, Texas from 1987 until 1997. We were on the cutting edge of gynecological surgery and in the mid-1990s we were doing laparoscopic Burch procedures with mesh. Within my group, several of us were interested in pelvic floor repair and went to cadaver labs with emphasis in pelvic anatomy. We were doing open uterosacral suspensions with paravaginal repairs and Burch procedures until I moved to Fairhope, Alabama, in 1998. At that time, I realized there was no one in our area who was interested in pelvic floor repair, although there was a large patient population with pelvic organ prolapse and incontinence. I continued with the open procedures until the year 2000,

when I became the first gynecologist in lower Alabama to do a classic transvaginal tape urethropexy (retropubic). After that, I became interested in the vaginal approach to pelvic prolapse and realized the significance for augmenting the repair because of the large failure rates from native tissue repair.[1] At that time, I used Pelvicol porcine fascia for my augmented repair, but I did have some issues with recurrence and was introduced to Gynemesh PS in 2002, at which time I went to training in Allentown, Pennsylvania. After the first Gynemesh PS cases, I completely switched to transvaginal mesh. I then became a preceptor for Gynecare and soon learned the transvaginal tape obturator approach to the sling procedure, and I was invited to the first cadaver lab/launch of Prolift in December 2004. In May 2005, I performed the first Prolift procedure in South Alabama and Panhandle of Florida, and after the first 20 cases I became a preceptor for Gynecare for all pelvic floor mesh and sling procedures. My last Prolift+M was in 2012, when it was taken off the market. I have trained many physicians from Alabama, Georgia, the Panhandle of Florida, Louisiana, Mississippi, and South Texas. I have given multiple talks, presentations, assisted with cadaver labs, and proctored physicians in their hospitals throughout the South. I have done approximately 1300 sling procedures for incontinence and over 700 procedures with either Gynecare PS, Prolift, Prolift+M, and/or Prosima.

III. INCIDENTS OF PELVIC ORGAN PROLAPSE DESCRIPTION EFFECT ON QUALITY OF LIFE.

A. What is prolapse?

1. Pelvic organ prolapse (POP), like urinary incontinence, is a common condition in women. Prolapse occurs when the pelvic organs, such as bladder, uterus, or rectum, descends or prolapses from its normal anatomical location in the vagina. The prevalence of prolapse increases with age as a major pelvic health concern as our population ages. The lifetime risk of surgery for POP in American women is 12.6%, and the combined rate of either stress incontinence or POP surgery is 20%, per a

[1] Benson JT, Lucente V, and McClellan E, Vaginal versus abdominal reconstructive surgery for the treatment of pelvic support defects: a prospective randomized study with long-term outcome evaluation. Am J Obstet Gynecol. 1996 Dec;175(6):1418-21.

study evaluating a large population base of more than 10 million women.[2] Risk factors for pelvic organ prolapse include age, menopause, parity (childbirth), genetics, neuropathy and myopathy, obesity, smoking, activity, and previous pelvic surgery.[3] Symptoms of pelvic organ prolapse include vaginal pressure with a bulging mass, urinary urgency and frequency, stress incontinence, voiding dysfunction, defecatory dysfunction ranging from fecal retention to incontinence, and coital difficulties.[4] Pelvic organ prolapse can be painful as well.

B. POP symptoms have a negative effect on quality of life.

1. The burden of urinary incontinence and prolapse on women is significant. Pelvic organ prolapse affects almost half of women over the age of 50 with a lifetime prevalence of 30% to 50%. The estimated annual cost of POP in the United States is more than $1 billion.[5]

2. Approximately 11% of American women will have an operation for incontinence and/or prolapse in their lifetime[6], as many as 300,000 pelvic floor reconstructive surgeries per year in the United States, and 29% to 40% of those will have their prolapse recur within 3 years of surgery.[7] The burden of untreated prolapse is significant. Studies have shown that POP adversely affects numerous aspects of women's quality of life, including social, psychological, physical, sexual, body image, and overall well being.[8] Prolapse can result in dyspareunia, vaginal pain, pelvic pain, and in the case of a rectocele (prolapsed rectum), constipation. Some

[2] Wu JM, et al., Lifetime risk of stress urinary incontinence or pelvic organ prolapse surgery. Obstet Gynecol. 2014 Jun;123(6):1201-6.
[3] Weber HM and Richter HE, Pelvic organ prolapse. Obstet Gynecol. 2005 Sep;106(3):615-34.
[4] Drutz HP and Alarab M, Pelvic organ prolapse: demographics and future growth prospects. Int Urogynecol J Pelvic Floor Dysfunct. 2006 Jun;17 Suppl 1:S6-9.
[5] Subak LL, et al., Cost of pelvic organ prolapse surgery in the United States. Obstet Gynecol. 2001 Oct;98(4):646-51.
[6] Fialkow MF, et al., Incidence of recurrent pelvic organ prolapse 10 years following primary surgical management: a retrospective cohort study. Int Urogynecol J Pelvic Floor Dysfunct. 2008 Nov;19(11):1483-7.
[7] Olsen AL, Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol. 1997 Apr;89(4):501-6.
[8] Rogers, GR, *International Urogynecology Journal*, (2010).

women, due to their prolapse, need to digitally "splint" in order to facilitate micturition and defecation.

IV. TREATMENT OPTIONS FOR POP

A. Conservative

1. Decision to treat pelvic organ prolapse is based on the number of organs prolapsed and more importantly on the patient's symptoms.

    a. Pelvic floor exercises, called Kegels, in some cases, can improve symptoms of prolapse. Also, pelvic floor physical therapy has shown improvement in pressure symptoms from pelvic organ prolapse.

    b. In many cases, weight loss, changes in diet, and avoidance of heavy lifting may improve symptoms of prolapse.

    c. A pessary is a vaginal support device that may help with pain and pressure of pelvic organ prolapse. It is a removable device, but in many cases, it is difficult to keep in place and patients may have dexterity issues that make it difficult to remove and clean adequately.

B. Surgery

Surgery is another treatment option for those with serious symptoms of pelvic organ prolapse, and women are more likely to have surgery if they have pain, significant pressure, daily activities are limited, and difficulty with intercourse. Surgery for pelvic organ prolapse may be performed by the transvaginal approach, open abdominal approach, and laparoscopic or robotic approach.

1. Native Tissue Repair

a. The most common type of surgery is a native tissue repair, which involves suspending the prolapsed structures using sutures or plicating the tissue over the prolapsing organ. Unfortunately, it has been associated with high

recurrence rates of 30% to 50%.[9] Sixty percent of the recurrences are identified at the same site.[10] Unmasking an occult support defect causes 32.5% of failures.[11] The healing and scarring caused by native tissue repair does not replace or add tensile strength, therefore it does not restore and maintain normal function.

b. The sacrospinous ligament fixation, iliococcygeus suspension, high uterosacral ligament suspension, and modified McCall culdoplasty are native tissue repairs that are commonly performed to treat apical vaginal prolapse or uterine prolapse. They involve using sutures to suspend the vaginal cuff or the uterus to other pelvic structures.

c. Anterior colporrhaphy is a native tissue repair of a patient's anterior vaginal wall. It involves plication of the vaginal fascia that overlies the bladder in order to reduce the prolapsing bladder. Native tissue anterior repairs have a high failure rate.

d. Posterior colporrhaphy is a native tissue repair of the posterior vaginal wall to repair a rectocele. Posterior colporrhaphy involves plicating the rectovaginal fascia in the midline, plication of the levator ani muscle (traditionally), and the trimming of any excess vaginal mucosa. In some posterior repairs—i.e., site-specific repairs—the levator ani muscle is not plicated. Studies have shown that posterior colporrhaphy can result in an increase in sexual dysfunction.[12]

e. Native tissue repairs are most often done vaginally, which reduces the morbidity of the procedure relative to repairs utilizing the abdominal approach, and, in turn, results in lower significant complication rates, shorter

[9] Vincent, JT, *American Journal of OB-GYN*, (2004).
[10] Marchione, et. al. *General Reproductive Medicine* (1999).
[11] Clark, et. al. *OB-GYN* (2003).
[12] Kahn MA and Stanton SL, Posterior colporrhaphy: its effects on bowel and sexual dysfuction. Br J Obstet Gynaecol. 1997 Jan;104:82-6; Komesu YM, et al., Posterior repair and sexual function. Am J Obset Gynecol. 2007 Jul;197:101.e1-101.e6; Karram M and Maher C, Surgery for posterior vaginal wall prolapse. Int Urogynecol J. 2013;24:1835-41.

hospital stays, less expense, less post-operative discomfort, and less blood loss.

f. In a 2016 Cochrane review, Dr. Christopher Maher and colleagues, the authors found that, when comparing native tissue repairs to repairs utilizing mesh, the patients receiving mesh were less likely to be aware of prolapse at one to three years after the surgery. They also found that rates of repeat surgery were lower in the group of patients treated with mesh, and that the patients treated with mesh were less likely to have recurrent prolapse on examination than were the patients who received native tissue repairs. They found no evidence of a difference between the mesh repair and the native tissue repair groups in the rate of de novo dyspareunia.[13] The Society of Gynecologic Surgeons Systematic Review Group authored a systematic review studying graft and mesh use in transvaginal prolapse repair, which was published in Obstetrics & Gynecology in 2016. They found that, in the anterior compartment, patients treated with synthetic nonabsorbable mesh consistently showed improved anatomic and bulge symptom outcomes compared to patients who were treated with native tissue repairs.[14]

g. Native tissue repairs present the same risks as do repairs augmented with polypropylene mesh. Mesh exposure, erosion, or extrusion does not occur with native tissue repairs because mesh is not used, but suture exposure, erosion, or extrusion can occur with native tissue repairs.[15] For instance, in the OPTIMAL trial, Barber and colleagues found that suture exposure occurred in connection with 15.4% of uterosacral ligament suspensions and

[13] Maher C, et al., Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse. Cochrane Database Syst Rev. 2016 Feb 9;2:CD012079.
[14] Schimpf MO, et al., Graft and Mesh Use in Transvaginal Prolapse Repair. Obstet Gynecol. 2016 Jul;128(1):81-91.
[15] Sokol AI, et al., One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse. Am J Obstet Gynecol 2012 Jan;86:e1-e9.

17.2% of sacrospinous ligament fixations 6-24 months after surgery.[16] Native tissue repairs present a potential risk of bleeding, organ damage (e.g., bladder, bowel, urethra, ureters), nerve damage, urinary frequency, dysuria, incontinence, urinary retention, urgency, acute pain, chronic pain, scarring, acute and/or chronic pain with intercourse, infection, neuromuscular problems, wound complications, fistula formation, recurrent prolapse, prolapse in an untreated compartment, contraction or shrinkage of tissues, and a foreign body response. Any of these complications, if they occur, can be temporary or permanent, and they can be mild, moderate, or severe, as any surgical complication can be. If any of these complications occur, they may result in the need for additional surgeries to treat the conditions, as is the case with any surgical complication. This is commonly known information among pelvic floor surgeons.

2. Augmented Repair

a. The general surgeons learned that an augmented graft had better results than a native tissue hernia repair.[17] Because of the poor outcomes frequently seen with native tissue repairs of pelvic organ prolapse, pelvic floor surgeons began to use grafts to augment their pelvic organ prolapse repairs. Over the years, many different types of grafts have been used—with varying degrees of success—to augment pelvic organ prolapse repairs.

i. **Allografts – (cadaver fascia)**. These are grafts typically made of cadaver fascia or dermis, which eliminates the morbidity and potential complications associated with the harvest of autologous fascia. The use of these grafts presents the same risks as listed above with respect to native tissue repairs. In connection with suburethral sling incontinence procedures, the use of cadaveric fascia lata

[16] Barber MD, et al., Comparison of 2 Transvaginal Surgical Approaches and Perioperatie Behavioral Therapy for Apical Vaginal Prolapse—The OPTIMAL Randomized Trial. JAMA 2014;311(10):1023-34, eTable 8—Adverse Events Related to the Surgical Outcome.

[17] Scott NW, et al., Open mesh versus non-mesh for repair of femoral and inguinal hernia. Cochrane Database Syst Rev. 2002;(4):CD002197.

allografts was associated with a material failure rate of ≥ 20%,[18] and has been shown to be fragmented, attenuated, or simply absent within 6-16 months of the surgery.[19] Fascia lata allografts and dermis have also been shown to retain donor antigens, DNA, or bacteria despite rigorous selection and sterilization, with unknown consequences.[20] Some patients voice cultural or religious objections to the use of cadaveric material in connection with their surgeries. Vaginal erosion of cadaveric fascia lata has been reported to occur in 23% of suburethral sling urethropexy surgeries and in 27% of sacrocolpopexies.[21]

ii. **Xenografts (porcine intestine or bladder).** These are tissues (intestine, bladder, fascia, or dermis), often from pigs or cows. The use of these grafts presents the same risks as listed above with respect to native tissue repairs. A systematic review in 2011 found that biologic grafts presented essentially the same risk of graft erosion as the use of non-absorbable synthetic grafts, and the risk of wound granulation tissue formation and dyspareunia was actually higher with biologic grafts.[22] Xenografts can become exposed or infected, and the potential for infectious disease transmission, while very low, cannot be completely eliminated. Some patients voice cultural or religious objections to the use of xenograft material in

[18] Fitzgerald MP, et al., Failure of allograft suburethral slings. BJU Int. 1999;84:785-88; Huang Y-H, et al., High failure rate using allograft fascia lata in pubovaginal sling surgery for female stress urinary incontinence. Urol. 2001;58(6):943-6; Soergel TM, et al., Poor Surgical Outcomes after Fascia Lata Allograft Slings. Int Urogynecol J. 2001;12:247-53.

[19] Carbone JM, et al., Pubovaginal sling using cadaveric fascia and bone anchors: disappointing early results. J Urol. 2001 May;165:1605-1611; Woodruff AJ, et al., Histologic Comparison of Pubovaginal Sling Graft Materials: A Comparative Study. Urology 2008;72:85-9.

[20] Fitzgerald MP, et al., The antigenicity of fascia lata allografts. BJU Int. 2000;86:826-28; Choe JM and Bell T, Genetic material is present in cadaveric dermis and cadaveric fascia lata. J Urol. 2001 Jul;166:122-4; Hathaway JK and Choe JM, Intact Genetic Materials Is Present in Commercially Processed Cadaver Allografts Used for Pubovaginal Slings. J. Urol. 2002 Sep; 168;1040-3.

[21] Kammerer-Doak DN, et al., Vaginal Erosion of Cadaveric Fascia Lata following Abdominal Sacrocolpopexy and Suburethral Sling Urethropexy. Int Urogynecol J 2002;13:106-09.

[22] Abed H, et al., Incidence and management of graft erosion, wound granulation, and dyspareunia following vaginal prolapse repair with graft materials: a systematic review. Int Urogynecol J. 2011 Jul;22(7):789-98.

connection with their surgeries. Studies have shown that xenografts used in pelvic floor surgery undergo severe encapsulation, preventing neovascularization or host infiltration.[23]

iii. Synthetics

a. Permanent (e.g., Gynemesh PS, Prolift). Synthetic mesh has been used in various surgical repairs for more than 50 years. It has been used to treat pelvic organ prolapse since the 1960s. Surgeons began using synthetic due to the poor outcomes seen with native tissue prolapse repairs. Initially, they free-hand cut the mesh to a desired shape and implanted it either abdominally or trans-vaginally. Ultimately, mesh "kit" devices like the Gynecare Prolift and Prosima were developed, which included pre-cut mesh and specially designed surgical tools used to facilitate the implantation of the mesh graft. The use of synthetic grafts presented the same risks associated with native tissue repairs, as discussed above. Synthetic mesh grafts' advantages include wide availability, no chance of infectious disease transmission, decreased chance of graft rejection possible with allograft and xenograft materials, consistency in quality, strength, and durability, and excellent tissue ingrowth. Various types of synthetic materials have been utilized as grafts, with many different types of construction (e.g., varying weights, pore sizes, knitted v. woven, etc.).

b. **Absorbable (e.g., Ultrapro, Prolift +M)**. Absorbable or partially absorbable meshes have been utilized as well, both in sheets that can be free-hand cut to a desired shape and in kits such as the Prolift +M device, discussed below. These

[23] Woodruff AJ, et al., Histologic Comparison of Pubovaginal Sling Graft Materials: A Comparative Study. Urology 2008;72:85-9.

meshes were developed in an attempt to increase patient comfort.

3. Transvaginal Mesh

a. The use of surgical mesh began with abdominal hernia repair. Much of this technology development inspired the innovation of transvaginal surgery. In the 1950s, Lane first recognized the need for graft augmentation for prolapse to improve disappointing surgical outcomes that existed at the time. Beginning in 1962, sacral colpopexy was introduced and performed. In 1998, the TVT device, which uses Prolene polypropylene (type 1 macroporous), was introduced and quickly became the gold standard procedure for stress incontinence. By the year 2002, polypropylene became the preferred graft material for a reinforced pelvic floor repair after the introduction of Gynemesh PS.

i. Gynemesh PS.

a. Gynemesh PS was cleared by the FDA on January 8, 2002, for its use in pelvic organ prolapse. It is a macroporous, type 1 monofilament polypropylene mesh. For the prolapse indication, it has a pore size of 2.4 mm and a light weight of 42 g/m^2. The Amid Mesh Classification was published in 1997 to classify hernia meshes,[24] and has been subsequently used to classify vaginal meshes as well. Gynemesh PS is a polypropylene mesh that has a pore size of greater than 75 microns, which is considered macroporous and desirable to allow passage of leukocytes and macrophages. The larger pore size allows capillary growth and integration of tissues into the pores that help support the prolapsed organ. Transvaginal mesh studies using Gynemesh PS began in

[24] Amid PK, Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia 1997;1:15-21.

2004 and reported data at six months. A later study presented data at one, three, and five years.[25]

b. De Tayrac and colleagues reported in 2001 on their use of Gynemesh in connection with cystocele repair with a mean follow-up of 13 months. They saw no post-operative infections in their 36 patients, one mesh exposure which was non-symptomatic, a 100% success rate in curing the cystocele, and an 86% cure rate for urinary incontinence.[26] Lucente and colleagues studied Gynemesh PS in 129 patients for one year and demonstrated efficacy and safety. They found a low rate of significant mesh-related complications, with a 76% success rate at 12-month follow-up.[27] Ali and colleagues conducted a randomized controlled trial of anterior colporrhaphy with and without Gynemesh PS and found that the use of Gynemesh PS reduced the recurrence rate of cystourethrocele from 11.6% to 6.6% (P>0.5) at 6-month follow-up, with a mesh erosion rate of 6.5%.[28] Collinet and colleagues conducted a retrospective study of 277 patients undergoing prolapse surgery—39% with Prolene mesh and 61% with Prolene Soft (i.e., Gynemesh PS). They observed a mesh exposure rate of 12.27% overall, with a rate of less than 1% when the uterus was preserved, although they did not specify what the exposure rate was with the Gynemesh PS.[29] In 2006, Dr. Sola and colleagues

[25] Jacquetin B, et al., Total transvaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 5-year prospective follow-up study. Int Urogynecol J 2013 Oct;24(10):1679-86.
[26] de Tayrac R, et al., Cystocele Repair with a Fixation-Free Prosthetic Polypropylene Mesh. Abs. 149.
[27] Lucente V, et al., A Clinical Assessment of GYNEMESH PS for the Repair of Pelvic Organ Prolapse. AUGS / SGS Oral Poster 55, 2004.
[28] Ali S, et al., A Prospective Randomized Trial Using Gynemesh PS for the Repair of Anterior Vaginal Wall Prolapse. Int Urogynecol J. 2006;17(Suppl. 2):S171-S359, Abs. 292.
[29] Collinet P, et al., Transvaginal mesh technique for pelvic organ prolapse repair: mesh exposure management and risk factors. Int Urogynecol J. 2006;17:315-20.

published the results of their prospective study of 31 patients treated with Gynemesh PS for repair of cystocele and rectocele. They observed no complications intra-operatively or post-operatively—no hematomas, infections, erosions, or de novo dyspareunia.[30] In 2006, Deffieux and colleagues performed a retrospective analysis of 34 consecutive cases of cystocele repairs using Gynemesh PS in which a mesh exposure occurred. They found that 59% of the patients required partial or complete excision of the mesh, which was successful in 77% of the cases. They concluded that management of vaginal mesh erosion was simple and associated with a low rate of morbidity.[31] Jo and colleagues reported on their study of 38 patients who underwent prolapse repairs using Gynemesh PS implanted transvaginally, and found a 94% cure rate at 18 months after surgery, with no erosions or infections.[32] Al-Nazer and colleagues published in 2008 an abstract of their comparative study of anterior colporrhaphy versus vaginal wall repair with Gynemesh or anterior vaginal wall prolapse, which noted that the patients treated with Gynemesh PS had a more significant improvement in their prolapse, urinary and sexual symptoms than did the patients who had a traditional anterior colporrhaphy with no mesh. They also found that operative morbidity was lower in the mesh group.[33] In 2008, Caquant and colleague, using the technique developed by the French TVM Group (discussed below), found that the use of

[30] Sola V, et al., Tension Free Monofilament Macropore Polypropylene Mesh (Gynemesh PS) in Female Genital Prolapse Repair. Int Braz J Urol. 2006 Jul-Aug;32(4):410-5.
[31] Deffieux X, et al., Vaginal mesh extrusion after transvaginal repair of cystocele using a prosthetic mesh: treatment and functional outcomes. J Gynecol Obstet Biol Reprod 2006;35:678-84.
[32] Jo H, et al., Efficacy and outcome of anterior vaginal wall repair using polypropylene mesh (Gynemesh). J Obstet Gynaecol Res. 2007 Oct;33(5):700-4.
[33] Al-Nazer MA, et al., Comparative study between anterior colporrhaphy versus vaginal wall repair with mesh for management of anterior vaginal wall prolapse. Int Urogynecol J. 2007;18(Suppl1):S25-S105, Abs. 084.

Gynemesh PS to cure genital prolapse via the vaginal route was reliable and easily reproduced. They noted an exposure rate of 11.3% overall, but only 4.7% when there was no concomitant hysterectomy performed.[34] Letouzey and colleagues reported in 2008 on their treatment of 63 women undergoing cystocele repair with Gynemesh PS, and found that none of the 54 patients followed for an average of 79 months required reoperation for cystocele recurrence, and there was a 16% vaginal extrusion rate. 80% of the patients were anatomically cured, and an additional 20% saw their prolapse improve.[35] Natale and colleagues reported in 2009 on the results of their prospective randomized controlled trial comparing Gynemesh and Pelvicol in the treatment of cystocele. They noted mesh erosion occurred in 6.3% of the Gynemesh PS patients, and an objective cure rate of 71.9% in the Gynemesh PS patients.[36] Dr. Marcus Carey and colleagues performed a prospective randomized controlled trial comparing vaginal repair with mesh versus colporrhaphy, the results of which were reported in 2009. They observed an 81% success rate in the mesh group and a 65.6% success rate in the colporrhaphy group. They found that the patients in both groups were highly satisfied with the surgery and improvements in their symptoms and quality of life at 12 months. Mesh exposure occurred in 5.6% of the patients. De novo dyspareunia occurred in 16.7% of the mesh patients and 15.2% of the colporrhaphy patients, but

[34] Caquant F, et al., Safety of Trans Vaginal Mesh procedure: Retrospective study of 684 patients. J Obstet Gynaecol Res. 2008 Aug;34(4):449-56.
[35] Letouzey V, et al., Long-Term Results after Trans-Vaginal Cystocele Repair Using a Tension-Free Polypropylene Mesh. J Minim Inv Gynecol. 2008;15:S1-S159, Abs. 102.
[36] Natale F, et al., A prospective, randomized, controlled study comparing Gynemesh, a synthetic mesh, and Pelvicol, a biologic graft, in the surgical treatment of recurrent cystocele. Int Urogynecol J. 2009;20:75-81.

the difference was not statistically significantly different.[37] In 2010, Young-Suk Lee and colleagues published the results of their study of 49 women who underwent trans-vaginal prolapse repair using Gynemesh PS, noting a 71.4% cure rate, with an additional 18.4% of the women with improvement of their prolapse. They saw only 1 case of vaginal mesh erosion.[38] In 2011, Dr. Dennis Miller and colleagues reported on their prospective multi-center long-term study on the use of Gynemesh PS using the technique developed by the TVM group. They observed a success rate in the treated compartment of 77.3%, and saw an exposure rate of 17.6%. De novo dyspareunia occurred in 3.5% at five-year follow-up.[39] Farthmann and colleagues reported on their randomized controlled trial involving the treatment of 200 patients with either a conventional mesh or partially absorbable mesh. They found that the exposure rate was lower in the patients receiving partially absorbable mesh (3.4% vs. 7.5%), but the rate of recurrent prolapse was also higher in those patients. The majority of all of the patients were fully satisfied with the surgery and had no pelvic floor pain.[40] In 2015, Samour and colleagues reported on the results of their retrospective study of 152 patients undergoing cystocele repair for grade 2 or more prolapse using Gynemesh. With respect to short-term post-operative side effects, they observed a 10.5% rate of severe post-operative

[37] Carey M, et al., Vaginal repair with mesh versus colporrhaphy for prolapse: a randomised controlled trial. BJOG 2009;116:1380-6.
[38] Lee Y-S, et al., Efficacy and Safety of "Tension-free" Placement of Gynemesh PS for the Treatment of Anterior Vaginal Wall Prolapse. INJ 2010;14:34-42.
[39] Miller D, et al., Prospective clinical assessment of the trans vaginal mesh (TVM) technique for treatment of pelvic organ prolapse – 5 year results. Female Pelvic Med & Reconstr Surg. 2010 Sept-Oct;16(5) (Suppl 2):S59, Paper 24.
[40] Farthmann J, et al., Lower exposure rates of partially absorbable mesh compared to nonabsorbable mesh for cystocele treatment: 3-year follow-up of a prospective randomized trial. Int Urogynecol J. 2013;24:749-58.

pain, but by the fourth post-operative day, all patients reported improved pain and no longer needed analgesics. They also saw two mesh erosions. At longer-term follow-up (median of 18.2 months), they saw significant improvement in most prolapse scoring parameters. Almost all patients (95%) were objectively considered cured based on the Ba cutoff value of ≥ 1. 90% of the patients reported that they felt cured based on the disappearance of a vaginal bulge, and another 8% felt an improvement. 90% of the patients reported that their sex life improved and that they felt more confident sexually after the cure of their prolapse. Only 3% had dyspareunia that persisted and impaired their sex life.[41] These studies, on the whole, report the safe and effective use of Gynemesh PS in treating pelvic organ prolapse.

ii. Prolift.

a. In 2000, a group of surgeons from France (TVM Group) put the concepts of the mesh and trocar systems together and created a new single, precut mesh to patch the vaginal wall weakness with mesh anchors.[42] The benefits of mesh kits over sutured mesh placement included decreased operative time, less extensive dissection, and more precise tensioning. It was important to standardize the surgical mesh kits because it was a way that pelvic surgeons could equalize outcomes. This group of nine accomplished French surgeons developed this product to evaluate the potential for incorporating the trocar delivery system to overcome the weaknesses of the suture-fixed transvaginal grafts. In 2002, they had over 300

[41] Samour H, et al., Minimally invasive cystocele repair technique using a polypropylene mesh introduced with the transobturator route. Arch Gynecol Obstet. 2015 Jan;291(1):79-84.
[42] Berrocal J, et al., Conceptual advances in the surgical management of genital prolapse. J Gynecol Obstet Biol Reprod 2004;33:577-87.

patients in the first study. By 2005, this study by Cosson, et. al. increased to include 687 patients. Ethicon then sponsored a prospective trial that would look at the results of Prolift over a one-, three-, and five-year period, and after approximately six months of data collection by Ethicon, Prolift was noted to be a safe and effective product for women.[43]

Table 1 Randomised controlled trials comparing polypropylene mesh with traditional native vaginal tissue repairs

Reference	Total number patients	Follow up (months)	Compartment studied	Anatomic cure mesh (%)	Anatomic cure traditional (%)	*p*
Hiltunen et al. [9]	104	12	Anterior	93	62	<0.04
Sivaslioglu et al. [10]	90	12	Anterior	91	72	<0.05
Nieminen et al. [11]	105	24	Anterior	89	59	<0.05
Nguyen and Burchette [12]	75	12	Anterior	87	55	<0.05
Carey et al. [13]	139	12	Anterior Posterior	81	65.6	0.07
Nieminen et al. [14]	202	36	Anterior	87	59	<0.0001
Withagen et al. [15]	194	12	All	90	55	<0.001
Altman et al. [16]	389	12	Anterior	82	48	0.008
Sokol et al. [17]	65	12	All	38	30	0.45

This table demonstrates multiple randomized controlled trials showing the transvaginal mesh was superior to traditional methods for pelvic organ prolapses.

b. Based on prelaunch trials with over 687 women with success rates of 89%, and exposure rates of approximately 13% with dyspareunia almost nonexistent, Ethicon considered Prolift as a safe and effective product.[44]

c. After Ethicon's launch of Prolift in 2005, we have seen multiple studies showing a superior success rate in mesh augmented repairs compared to native tissue. It is important

[43] Jacquetin B, et al., Total transvaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 5-year prospective follow-up study. Int Urogynecol J 2013 Oct;24(10):1679-86.
[44] Cosson M, et al., Prolift (Mesh (Gynecare) for Pelvic Organ Prolapse Surgical Treatment Using the TVM Group Technique: A Retrospective Study of 687 Patients. ICS Abstract 121, 2005.

to note that De novo dyspareunia is no greater following Prolift than when compared to native tissue. Much of this data is from multi-center, randomized trials, which is one of the highest levels of scientific evidence.[45] Compared to native tissue repair, with the use of a permanent polypropylene mesh, such as Gynemesh PS, there is no difference in repeat surgery for incontinence or dyspareunia.

d. Dr. Mariëlla Withagen and colleagues published the results of a randomized controlled trial comparing patients treated with Prolift with those treated with conventional vaginal prolapse surgery in 2011. At 12 months' follow-up, there was anatomic failure in 45.2% of the patients in the conventional group but only in 9.6% of the mesh group. Subjective improvement was very similar, at 80% in the conventional group and 81% in the mesh group. Mesh exposure was observed in 16.9% of patients, and quality of life improvement was equal in both groups. Dyspareunia decreased in both the mesh and non-mesh patients at twelve-month follow-up, and de novo dyspareunia was not statistically significantly different between the groups (8% mesh vs. 10% non-mesh). Lower abdomen or genital area pain decreased at one-year follow-up compared to baseline, and was not statistically significantly different between the groups. De novo lower abdomen or genital area pain occurred in 7.5% of the patients in the mesh group and in 4% of the patients in the non-mesh group, but the difference was not statistically significantly different.[46]

[45] Oxford Levels of Evidence for Practitioners.
[46] Withagen MI, et al., Trocar-Guided Mesh Compared With Conventional Vaginal Repair in Recurrent Prolapse: A Randomized Controlled Trial. Obstet Gynecol. 2011 Feb;117(2):242-50.

e. Dr. Daniel Altman and colleagues, for the Nordic Transvaginal Mesh Group, reported in 2011 on the results of their multicenter, parallel-group, randomized controlled trial comparing the use of Prolift and traditional colporrhaphy for cystocele repair in 389 patients. At one-year follow-up, the primary outcome—a composite of POP-Q Stage 0-1 and the subjective absence of vaginal bulging symptoms—was significantly more common in the women treated with Prolift (60.8%) than it was in women treated with traditional colporrhaphy (34.5%). 3.2% of the 186 patients in the Prolift group had surgical re-intervention to correct mesh exposure. Persistent pain was present in one of the 186 patients at one-year follow-up. A greater percentage of patients in the mesh group had dyspareunia, but the overall reported rate of dyspareunia and satisfaction with sex life was similar in the two treatment groups. Pelvic or genital pain occurred in only one patient in the mesh group.[47]

f. In 2012, Dr. Michael Halaska and colleagues reported on the results of their multi-center randomized controlled trial comparing Prolift repair with a sacrospinous ligament fixation. They found that prolapse recurred in 39.4% of the sacrospinous ligament fixation patients and in 16.9% of the Prolift patients (P = .003). Mesh exposure occurred in 20.8% at one-year follow-up, and one quarter of those patients with exposures were symptomatic. There was no difference in quality of life improvement between the two groups. The

[47] Altman D, et al., Anterior Colporrhaphy versus Transvaginal Mesh for Pelvic-Organ Prolapse. N Engl J Med 2011;364:1826-36.

rates of dyspareunia and pelvic pain did not statistically significantly differ between the two groups.[48]

g. In 2012, Dr. Andrew Sokol and colleagues published the one-year results of their randomized controlled trial comparing mesh-augmented colpopexy with traditional colpopexy. They saw a 15.6% mesh exposure rate, but a 15% of apical Gore-Tex suture exposure in the non-mesh group. POP-Q measurements improved in both groups. Quality of life improved in both groups (96.2% mesh vs. 90.9% non-mesh) but did not statistically significantly differ. Both groups of patients had high subjective satisfaction with the surgery at one-year follow-up, and sexual function improved significantly in both groups with no significant difference between the groups at one-year follow-up. There was no statistically significant difference between the mesh group and the non-mesh group with respect to de novo dyspareunia (9.1% mesh v. 21.4% non-mesh).[49]

h. In a retrospective study published in 2012, which followed patients for 4.5 years, Dr. Sabrina Benbouzid and colleagues observed an 85.3% cure rate with Prolift use, and a mesh exposure rate of only 5.3%. Three patients (10%) reported de novo dyspareunia, but four patients who had pre-existing dyspareunia saw their symptoms improve after surgery. The study also summarized the cure rates and mesh exposure

[48] Halaska M, et al., A multicenter, randomized, prospective, controlled study comparing sacrospinous fixation and transvaginal mesh in the treatment of posthysterectomy vaginal vault prolapse. Am J Obstet Gynecol. 2012;207:301.e1-7.
[49] Sokol AI, et al., One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse. Am J Obstet Gynecol 2012; 206:86.e1-9.

rates from prior published studies, which show good cure rates and mesh exposure rates ranging from 0%–15%.[50]

i. That same year, Dr. Laurent de Landsheere and colleagues reported on their retrospective single-center study involving 524 patients with a median follow-up of three years. They found the global re-operation rate after Prolift surgery was 11.6%, with urinary incontinence surgery being the most common indication. One patient out of 524 (0.2%) presented with mesh infection after a total Prolift mesh repair with concomitant hysterectomy. Mesh exposure occurred in thirteen of 524 patients (2.5%).[51]

[50] Benbouzid S, et al., Pelvic organ prolapse transvaginal repair by the Prolift system: Evaluation of efficacy and complications after a 4.5 years follow up. Int J Urol 2012;19:1010-1016.
[51] De Landsheere L, et al., Surgical intervention after transvaginal Prolift mesh repair: retrospective single-center study including 524 patinets with 3 years' median follow-up. Am J Obstet Gynecol 2012;206:83.e1-7.

Table 5 Results of Prolift surgery according to the previous literature

Series (reference)	No. patients	Device	Type	Mean follow up	Cure rate (anatomical)	Mesh exposure	Study design
Present series	75	Prolift	Anterior: 51 Posterior: 3 Total: 20	54 months	81.5%	5.3%	Retrospective
de Landsheere 2011[14]	526	Prolift	Anterior: 48 Posterior: 103 Total: 373	38 months†	N/A	3.6%	Retrospective
Vaiyapuri 2011[16]	254	Prolift	Anterior: 106 Posterior: 20 Total: 128	12 months	95.6%	11.5%	Retrospective
Milani 2011[17]	127	Prolift+M	Anterior: 41 Posterior: 16 Total: 70	12 months	77.4%	10.2%	Prospective
Huang 2011[13]	65	Prolift	Total: 65	24.5 months†	94%	2%	Retrospective
Wetta 2009[18]	50	Prolift	Anterior: 16 Posterior: 16 Total: 18	14 months	98%	2%	Prospective
Van Raalte 2010[19]	91	Prolift	Anterior: 46 Posterior: 28 Total: 23	19 months†	86.6%	0%	Prospective
Nair 2011[20]	60	Prolift	Anterior: 21 Posterior: 12 Total: 27	29 months	85%	15%	Prospective
Elmer 2009[21]	252	Prolift	Anterior: 121 Posterior: 68 Total: 63	12 months	80%	11%	Prospective
Hollander 2010[23]	323	Prolift	Anterior: 88 Posterior: 91 Total: 144	20 months	87%	11.5%	Retrospective

†Median follow up.

j. Dr. Robert Gutman and colleagues published in 2013 the three-year results of their randomized controlled trial comparing colpopexy prolapse repair with and without mesh. 33 patients in the study had a mesh repair, and 32 had a traditional repair. The investigators stopped the study early due to a 15.6% mesh exposure rate, and they saw no statistically significant difference in cure rates between the two groups. They found cure rates in the anterior wall higher in the mesh group, but not significantly so. When the hymen was used as a threshold for anatomic cure, 85% of the mesh patients were considered cured and 71% of the non-mesh patients. 92% of the mesh patients and 81% of the non-mesh patients had no bulging and protrusion symptoms. The study

also showed an overall high rate of recurrence in both the mesh and non-mesh patient groups. Sexual function did not differ between the two groups, and overall quality-of-life improvement in both groups was high.[52]

k. In a multi-center randomized trial comparing native tissue repair and Prolift repair, Dr. Simone dos Reis Brandão da Silveira and colleagues reported that at one-year follow-up, anatomical cure rates were better in the mesh group in the anterior compartment. Both groups had significant improvement in quality-of-life scores, with a greater improvement in the mesh group. The mesh group had a 3.4% dyspareunia rate, while the non-mesh group had a 6.2% rate, but there was no statistically significant difference between the group. 8.6% of the non-mesh patients had pain, whereas only 2.3% of the Prolift patients did. There was a 20.5% extrusion rate, but most of those patients' extrusions were treated with topical estrogen.[53]

l. In 2015, Svabik and colleagues published the results of a single-center randomized controlled trial comparing Prolift use and sacrospinous ligament fixation to treat post-hysterectomy vaginal vault prolapse. At one-year follow-up, they observed a 3% rate of anatomical failure in the Prolift group and a 65% anatomical failure rate in the sacrospinous ligament fixation group. They also saw a non-statistically significant but greater improvement in POPDI scores in the Prolift group. They observed an 8% rate of minor mesh exposure at three-month follow-up, two of which were

[52] Gutman RE, Three-Year Outcomes of Vaginal Mesh for Prolapse: A Randomized Controlled Trial. Obstet Gynecol. 2013 Oct;122(4):770-7.
[53] Dos Reis Brandão da Silveira S, et al., Multicenter, randomized trial comparing native vaginal tissue repair and synthetic mesh repair for genital prolapse surgical treatment. Int Urogynecol J. 2015 Mar;26(3):335-42.

resected, and no additional cases of exposure at the one-year follow-up. 15% of the patients in the native tissue repair group had vaginal blood spotting due to granulation tissue. Sexual function and dyspareunia did not significantly differ between the two groups of patients.[54]

m. Damoiseaux and colleagues published an abstract of their 7-year randomized controlled trial of prolapse repair with Prolift versus conventional repair. They noted an unusually high mesh exposure rate (40%), but pain, chronic pelvic pain, de novo pelvic pain, and de novo dyspareunia were still lower (although not statistically significantly so) in the mesh group.[55]

n. According to the most recent Cochrane Review, the use of a permanent polypropylene mesh demonstrates a lower rate of awareness of prolapse, reoperation for prolapse, and prolapse on examination in contrast to native tissue repair.[56] Many of these studies on Gynemesh PS and Prolift demonstrate an overall positive effect on sexual function with many having dyspareunia at baseline, which resolves after surgery. This is consistent with the findings by Dietz and Maher whose review found no difference in postoperative, de novo dyspareunia, or change in sexual function as assessed by the PISQ survey for mesh versus native tissue repair.[57] Dr. Joye Lowman and colleagues published a study in 2008 analyzing

[54] Svabik K, et al., Comparison of vaginal mesh repair with sacrospinous vaginal colpopexy in the management of vaginal vault prolapse after hysterectomy in patients with levator ani avulsion: a randomized controlled trial. Ultrasound Obstet Gynecol 2014 Apr;43(4):365-71.
[55] Damoiseaux A, et al., Long-term follow-up (7 years) of a randomized controlled trial: trocar-guided mesh compared with conventional vaginal repair in recurrent pelvic organ prolapse. Int Urogynecol J. 2016;26 (Suppl 1):S23-S174, PP 01.
[56] Maher C, et al., Transvaginal mesh or grafts compared with native tissue repair for vaginal prolapse. Cochrane Database Syst Rev. 2016 Feb 9;2:CD012079.
[57] Dietz V and Maher C, Pelvic organ prolapse and sexual function. Int Urogynecol J 2013;24:1853-7..

whether the Prolift system causes dyspareunia, and found that the rate of de novo dyspareunia was 16.7%. The authors also noted, however, that other procedures involving native tissue prolapse repairs or abdominally placed mesh also have been reported to have comparable if not higher rates of dyspareunia, as shown in Table 4 of the study, reproduced below.

TABLE 4
De novo dyspareunia after prolapse surgery

Dyspareunia	ASC N = 224 (148)[a] Handa et al[21]	SSLF N = 287 (106)[a] Maher et al[6]	USS N = 110 (34)[a] Silva et al[27]	APR N = 165 (81)[a] Weber et al[18]	Prolift N = 129 (57)[a]
Baseline (preop) dyspareunia (%)	40.5 (60/148)	Unknown	20.6 (7/34)	8.0 (6/81)	36.8 (21/57)
De novo (postop) dyspareunia (%)	14.5 (11/76)	36.1 (22/61)	25.9 (7/27)	19.0 (14/75)	16.7 (6/36)

[a] Number sexually active preop.

Lowman. Does the Prolift system cause dyspareunia? Am J Obstet Gynecol 2008.

They also noted that dyspareunia is commonly reported in reproductive-aged women, menopausal women, and especially in women with pelvic floor disorders.[58] Likewise, in the systematic review published in 2011 by the Systematic Review Group of the Society of Gynecologic Surgeons, it was noted that dyspareunia occurred in connection with 8.9% of synthetic graft prolapse repairs and in 9.6% of biological graft prolapse repairs.[59] That study by the SGS Systematic Review Group also showed similar erosion rates between synthetic graft repairs and biological graft repairs—10.3% and 10.1%, respectively.

[58] Lowman JK, et al., Does the Prolift system cause dyspareunia? Am J Obstet Gynecol 2008;199:707.e1-707.e6.
[59] Abed H, et al., Incidence and management of graft erosion, wound granulation, and dyspareunia following vaginal prolapse repair with graft materials: a systematic review. Int Urogynecol J. 2011 Jul;22(7):789-98.

o. Mesh exposure is the only unique complication with Gynemesh PS and Prolift, although as noted above, other wound complications occur without the use of mesh.[60] In most cases these exposures can be treated conservatively with vaginal estrogen or simple excision in the office; however, none are associated with recurrence of prolapse.

p. In 2016, the Society for Gynecologic Surgeons Systematic Review Group published a review of literature regarding graft and mesh use in transvaginal prolapse repair. In the anterior compartment, they found that "synthetic nonabsorbable mesh use consistently showed improved anatomic bulge system outcomes compared with native tissue repairs based on meta-analyses." They found that other subjective outcomes, such as dyspareunia and urinary incontinence, generally do not differ between the two groups. In the posterior compartment, they found that synthetic mesh use did not improve success. Mesh exposure rates range from 1.4% to 19% in the anterior compartment and between 3% and 36% when the mesh was placed in multiple compartments. Overall, operative mesh exposure rates range from 3% to 8%.[61]

q. In a retrospective Canadian study, 5,488 women who underwent mesh-based prolapse procedures between 2002 and 2013, showed that 5% of women who underwent a mesh-based prolapse surgery required a reoperation for mesh

[60] Murphy M, et al., Time to rethink: an evidence-based response from pelvic surgeons to the FDA Safety Communication: "UPDATE on Serious Complications Associated with Transvaginal Placement of Surgical Mesh for Pelvic Organ Prolapse." Int Urogynecol J 2012 Jan;23(1):5-9.
[61] Schimpf MO, et al., Graft and Mesh Use in Transvaginal Prolapse Repair, Obstet Gynecol. 2016 Jul;128(1):81-91.

complications within 10 years.[62] Prolift studies have more patients along with follow-up than native tissue repair. The clinical data is clear that Prolifts can be performed safely and effectively with results that approach the gold standard procedure abdominal sacrocolpopexy.

iii. Prolift+M

a. In 2009, Ethicon added monocryl poliglecaprone 25 suture material to the permanent mesh to improve intraoperative handling. This was designed to resist the wrinkling and folding of the mesh.[63,64,65] This innovation was thought to decrease foreign body response exhibiting 55% less inflammation to the surrounding tissue compared to polypropylene. It also resulted in 46% less mesh at 84 days which improved tissue ingrowth. The mesh used was Gynecare's Ultrapro mesh, and the device was implanted according to the same procedure as used with the Prolift device, using the same tools. Prior to the absorption of the Monocryl component over the course of 90-120 days, the pore size of the mesh was 3.5 mm and the weight was 57g/m^2. Once the Monocryl component was absorbed, the pore size was 2.5 mm, and the weight was 31 g/m^2.[66]

b. The preclinical animal studies of the use of Ultrapro mesh showed a reportedly greater distance between pores decreasing risk of bridging fibrosis.[67] The overall anatomic

[62] Kelly EC, Winick-Nj J, Welk B, Surgeon Experience and Complications of Transvaginal Prolapse Mesh. Obstet Gynecol. 2016 Jul;128(1):65-72.
[63] Jung, et. al., *Hernia* (2005)
[64] Kling, et. al., Shrinkage of Polypropylene Mesh In Vivo, *European General Surgeon Journal Surgery* (1998).
[65] Laschke, et.al., *Journal of Biomed Material* (2005).
[66] Khandwala S, Transvaginal Mesh Surgery for Pelvic Organ Prolapse: One-Year Outcome Analysis. Female Pelvic Med & Reconstr Surg. 2013 Mar/Apr;19(2):84-89.
[67] Khandwala S, Transvaginal Mesh Surgery for Pelvic Organ Prolapse: One-Year Outcome Analysis. Female Pelvic Med & Reconstr Surg. 2013 Mar/Apr;19(2):84-89; Cobb, W, *Journal of Surgical Research* (2006).

success rates of Prolift and Prolift+M was evaluated by Sikirica in 2008.[68] It showed, in 1976 patients, a 90% anatomic success rate. The pelvic floor repair system is built on a proven delivery system but uses the new mesh. This study, by Piet Hinoul and the investigators of Prolift+M, revealed that the new mesh characteristics still provided the same strong support of the mesh as in the original Gynecare Prolift System.

c. In 2011, Dr. Alfredo Milani and colleagues—including Dr. Piet Hinoul, Judi Gauld, and Vanja Sikirica from Ethicon—published the results of a prospective multi-center cohort study involving 127 patients treated with Prolift+M. They found anatomic success (which they defined as prolapse ≤ stage I in the treated compartments) was 77.4%, and significant improvements in bother, quality of life and sexual function were seen at three and twelve months compared with baseline. 86.2% of the patients thought their prolapse was "much better" one year after the surgery. 91.2% of the patients had bulge symptoms before surgery, and only 8.9% did at one-year follow-up. 10.2% of the patients experienced a mesh exposure, and the rate of de novo dyspareunia was 2%. The one case of post-operative de novo dyspareunia was attributed to vaginal dryness. Before the surgery, 66 patients were not sexually active, and after the surgery, nine of those patients resumed sexual intercourse without experiencing any new-onset dyspareunia.[69]

d. Milani and colleagues published an abstract in 2012 of their medium-term outcomes from the same Prolift +M study discussed above. At three-year follow-up, the anatomic

[68] Sikirica (2008).
[69] Milani AL, et al., Trocar-guided mesh repair of vaginal prolapse using partially absorbable mesh: 1 year outcomes. Am J Obstet Gynecol 2011;204:74.e1-8.

success rate (defined the same way) was 75.9%. 88% of the patients had the leading vaginal edge above the hymen in the treated compartment. Quality of life significantly improved. Mesh exposure occurred in 14.8% of patients, and de novo dyspareunia occurred in 9% of patients, while pre-existing dyspareunia resolved in 33% of the patients with pre-existing dyspareunia.[70]

e. In 2012, Bhatia and colleagues reported on the results of a retrospective cohort study measuring sexual health following surgery with Prolift and Prolift+M. Sexual function outcomes were measured by the PISQ-12 questionnaire, and showed that PISQ scores improved significantly in both the Prolift and Prolift+M. They found that there was a significant improvement in post-operative sexual desire, comfort with intercourse, and overall sexual function with the Prolift+M compared to the Prolift at four months, but the significance was not found at twelve months.[71]

f. In 2013, Dr. Salil Khandwala reported on his prospective cohort study of patients treated with Prolift+M. Out of 157 patients followed for thirteen months, he observed a composite success rate of 88.1%, with a pure anatomic success rate based on POP-Q scores < II of 94%. Mesh exposure occurred in 2.2% of patients (only one of which underwent excision in the operating room), and de novo dyspareunia occurred in 6%.[72]

[70] Milani AL, et al., Medium-term clinical outcomes following trocar-guided mesh repair of vaginal prolapse using partially absorbable mesh. Int Urogynecol J 2012;23(Suppl 2):S43-S244, Abs. 81.
[71] Bhatia N, et al., A Comparison of sexual function outcomes 1 year after undergoing a transvaginal mesh procedure using polypropylene mesh vs. hybrid polypropylene/poliglecaprone mesh. Female Pelvic Med & Reconstr Surg. 2012 Mar/Apr;18(2)(Suppl 1), Oral Poster 19.
[72] Khandwala S, Transvaginal Mesh Surgery for Pelvic Organ Prolapse: One-Year Outcome Analysis. Female Pelvic Med Reconstr Surg 2013;19:84-89.

g. Dr. Julie Quemener and colleagues reported on the results of their twenty-month follow-up study of Prolift+M use in 250 patients in 2014 in the European Journal of Obstetrics & Gynecology and Reproductive Biology They observed a 2% mesh exposure rate and a global rate of re-operation of 8% for various complications or recurrence. They found small but non-statistically significant differences in the rates of mesh-related complications, mesh exposure, prolapse recurrence, and urinary complications between their Prolift patients and their Prolift+M patients.[73]

h. Overall, these studies show that Prolift +M is safe and effective, but not more so than Prolift.

iv. Prosima.

a. The Prosima device was introduced as a trocar-less system that utilized Gynemesh PS and the vaginal support device (VSD) for moderate (POP-Q stages II-III) symptomatic pelvic organ prolapse. Included with the mesh implant was an inserter instrument that facilitated the implantation of the mesh, as well as a vaginal support device (VSD) and balloon assembly. The VSD supported the vaginal tissues after surgery, facilitating abutment of the vaginal tissues against the mesh, thereby promoting tissue ingrowth. The inflated balloon replaces traditional gauze packing and fills the vaginal cavity and abuts the mesh implant(s) in the vagina in the first day after surgery, while the VSD remains in place for three-to-four weeks post-operatively. Unlike gauze, the inflatable balloon did not shrink with blood absorption, and could be removed with less pain or discomfort than gauze. The VSD could be trimmed so as to best fit the patient's

[73] Quemener J, et al., Rate of re-interventions after transvaginal pelvic organ prolapse repair using partially absorbable mesh: 20 months median follow-up outcomes. Eur J Obstet Gynecol Reprod Biol 2014;175:194-98.

anatomy. The mesh in the Prosima device was Gynemesh PS—the same knitted, macroporous, monofilament, lightweight mesh used in the Prolift device, made of Prolene polypropylene. The mesh was pre-cut, with pockets on the mesh that facilitated its implantation with the included inserters. All of these attributes and characteristics of the Prosima device were useful and helpful to the surgeon. The device could be implanted with a single incision, avoided deep passes and the use of cannulae, and involved less dissection than other pelvic organ prolapse mesh kits.

b. Like Prolift, it underwent many years of study with development and testing of surgical technique, prototype, and mesh configuration. Studies began in 2004, and the device was not introduced until more than five years later. Over time, the device and technique were honed to provide a safe and effective method.[74] The 12- and 24-month Prosima study results demonstrated good efficacy in a positive safety profile.[75] The anatomic cure rate was a little less than seen with Prolift; however, there was a high degree of an absence of awareness of a vaginal bulge, and patient satisfaction was 87%. There were several studies of Prosima which demonstrated its efficacy and safety. Rates of objective anatomic cure reported, generally, an 80% to 95% range with accompanying significant improvement in subjective measures, symptoms, quality of life, a lower reoperation rate, a low rate of de novo dyspareunia with positive effect on the sexual function, and resolution of pre-existing dyspareunia.

[74] Kerry, M, *Medical Journal of Obstetrics & Gynecology* (December 2010).
[75] Zyczynski HM, et al., One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device. Am J Obstet Gynecol 2010;203:587.e1-8; Sayer T, et al., Medium-term clinical outcomes following surgical repair for vaginal prolapse with tension-free mesh and vaginal support device. Int Urogynecol J 2012 Apr;23(4):487-93.

Rates of mesh exposure ranged from 0% to 15% which were acceptable and in many cases can be treated with estrogen.[76] Overall, like Gynemesh PS and Prolift, the Prosima device is safe and effective and useful in treating moderate prolapse with no inherent defects.[77]

c. Zyczynski and colleagues—including Judi M. Gauld, Dr. David Robinson, and Vanja Sikirica of Ethicon—reported on the one-year clinical outcomes after Prosima surgery in 2010. Their study involved 136 women, and they found that 76.9% of the women had prolapse of ≤ stage I, and 86.9% of the women had the leading vaginal edge above the hymen. Pelvic symptoms, quality of life, and sexual function significantly improved compared to pre-surgery. Out of the eleven women who had dyspareunia before the surgery, nine of them reported that it resolved by one year after the surgery. De novo dyspareunia occurred in three women, but twelve women who were not sexually active before surgery resumed sexual intercourse without de novo dyspareunia after the surgery. Mesh exposure occurred in 8% of the patients.[78]

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[76] D'Afiero A, Short-term effects of mesh augmented surgery for pelvic organ prolapse on functional outcomes and QOL: a comparison between trocar guided and single incision devices. Int J Gynecol & Obstet. 2012;11953:S261-S530, Abs. 0156.

[77] Tsai CP, et al., Factors that affect early recurrence after prolapse repair by a nonanchored vaginal mesh procedure. Taiwan J Obstet Gynecol. 2014 Sep;53(3):337-42; Chen J, et al., Prospective study on total pelvic reconstruction surgery with Prosima in the treatment of pelvic organ prolapse stage III. Chinese J Obstet Gynecol 2012;47(9):664-68; Bezhenar V, Guseva E, The Pelvic Floor Repair with the Use of Prosima Implant – The Assessment of Complications and Life Quality. ICS 2013 (Abs. 765); Hung M, Tsai C, Suboptimal Suspension Effect of the Prosima Procedure for Severe Anterior Vaginal Wall Prolapse. Int Urogynecol J 2012;23 (Suppl 2):S43–S244 (Abs. 149); Khandwala S, et al., A Trocar-Free Procedure for Vaginal Prolapse Repair Using Mesh and a Vaginal Support Device – An Observational Registry. Female Pelvic Med & Reconstr Surg 2011 Sept/Oct;17(5) (Suppl. 2):S164; Singh R, et al., Anatomic, Functional and Ultrasound Outcomes After Vaginal Prolapse Surgery Using Non-Anchored Mesh. (Abs. 575) 2011; Reisenauer C, et al., Anatomical Cadaver Study of Pelvic Floor Reconstruction Using a New Polypropylene Implant Vaginal Repair System and a Vaginal Support Device. Int Urogynecol J 2009;20(Suppl 2):S73–S239.

[78] Zyczynski HM, et al., One-year clinical outcomes after prolapse surgery with nonanchored mesh and vaginal support device

d. Dr. Sayer and colleagues reported on the medium-term outcomes of the same study of 136 women (median follow-up of 29 months), and found the primary anatomic success rate (defined as POP-Q stage ≤ I) was 69.1%, but that in 84.5% of the cases, the leading vaginal edge was above the hymen. There were significant improvements in pelvic symptoms and sexual function, and the mesh exposure rate was 9.1%.[79]

V. PELVIC ORGAN PROLAPSE (INFORMATION PROVIDED TO PHYSICIANS)

A. Ethicon was quite diligent in making information, live surgical instruction, cadaver labs, and proctorships available for surgeons learning how to use all the POP products. Not only were surgeons sent to training, which included cadaver labs and didactic presentations, they were also sent to work with proctors, and in my case, the physicians trained in the operating room were able to scrub in the procedure. They were given the option to be proctored at their own hospital for a number of cases as specified by their credential committee. Ethicon went further and produced a Surgeon's Resource Monograph regarding the Prolift device, which would even discuss complications studies that were available and pearls to techniques to aid in the physician's successful surgical repair. The IFUs that are available for Gynemesh PS, Prolift, Prolift+M, and Prosima were more than adequate, and helped surgeons use the devices safely. But as an experienced surgeon will tell you, the hands-on experience is more effective at perfecting a surgery than simply reading instructions. The IFU builds on the knowledge that we, as pelvic surgeons, have acquired through our prior education and experience and warrants that users should be pelvic floor surgeons and familiar with the surgical procedures and techniques regarding pelvic floor repair and nonabsorbable meshes before using the device. One must bear in mind that the audience for an IFU is a pelvic floor surgeon who has gone through medical school, a residency, and in some cases a fellowship, and regularly reviews published medical literature discussing pelvic floor surgery and the complications associated with it. Surgeons also often attend professional organization or

[79] Sayer T, et al., Medium-term clinical outcomes following surgical repair for vaginal prolapse with tension-free mesh and vaginal support device. Int Urogynecol J 2012 Apr;23(4):487-93.

society meetings and learn about various pelvic floor surgeries in those meetings, or in discussions with colleagues. They are aware of the potential risks of native tissue repairs and graft augmented repairs, and know that they are—with the exception of mesh exposure/erosion—the same risks.[80] However, as noted above, exposure and erosion of permanent sutures and biologic grafts also occur. These risks associated with native tissue repairs and graft augmented repairs are commonly known among pelvic floor surgeons, and in my opinion, do not need to be individually itemized in the IFU of the product. It is neither helpful nor necessary, in my opinion, for device IFUs to list risks that are commonly known.[81] Furthermore, surgeons know that any complications that occur following a surgery can be temporary or permanent, and they can be mild, moderate or severe. It is not necessary for an IFU to provide that information. Nor is it necessary for the IFU to specify the frequency with which various complications occur. Those rates are published in the medical literature that surgeons regularly review, they vary significantly in some instances, and are often changing. The treatment of complications following mesh implantation surgery is something that surgeons learn in residency and fellowship, and something surgeons know how to do based on their familiarity with the female anatomy and their training.

B. The topics included in the Surgeon's Resource Monograph included the following:

- Patient selection
- Preparation
- Surgical technique
- Anesthesia
- Hydrodissection

[80] American Board of Obstetrics and Gynecology, Inc., Guide to Learning in Female Pelvic Medicine and Reconstructive Surgery 2012 (fellows will discuss the alternatives, risks, benefits, complications, success rates, and levels of evidence for various surgical treatments of pelvic organ prolapse, including vaginal mesh procedures); AUGS Resident Learning Objectives (residents should understand the possible complications of surgical correction of pelvic organ prolapse and be able to counsel the patient on treatment plan, including side-effects, risk, failure, and complications); Accreditation Council for Graduate Medical Education Program Requirements for Graduate Medical Education in Female Pelvic Medicine and Reconstructive Surgery Pt. IV.A.5.b).(2).(c) (fellows completing the F2 year must demonstrate competence in their knowledge of contraindications, limitations, indications, complications, techniques, and interpretation of results of screening, diagnostic, and therapeutic procedures including surgery for pelvic organ prolapse and urinary incontinence).

[81] 21 C.F.R. Part 801(c); FDA Device Labeling Guidance #G91-1 (blue book memo); Ethicon Franchise Regulatory Labeling Guidance § 6.1.2 ("Labeling must convey the information that end-users need to safely use the device as intended by the manufacturer, taking into account the conditions of use and any issues that may be specific to the type of device.")

- Incisions
- Uterine conservation
- Additional sutures
- Mesh handling
- Technical pearls
- Concomitant procedures
- Postoperative care
- Complications
    - There are 7 active case series with interim results available. Complications rates within those series are low and will continued to be reviewed. The most notable complications are listed below:
        - Intraoperatively:
            - Hemorrhage
            - Visceral injury
            - Ureteral obstruction.
        - Postoperatively:
            - Hemorrhage
            - Hematoma
            - Fistula
            - Infection
            - Urinary retention
            - Mesh exposure
            - Dyspareunia
            - Vaginal pain.
                - Each of these postoperative complications were detailed and discussed at length including a clinical data summary of complications. These were all abstracts from the International l Urogynecology Association (IUGA) 2006 and The American Urogynecologic Society (AUGS) 2006.

CLINICAL DATA Summary

Author	Patients	Follow-up	Exposure*	Success	Complications
Cosson et al	90	12 mo	9 (10%) 5 (5.6%)	74 (81.6%)	Rectal injury 1 Bleeding 2 Fistula (VV) 1
Fatton et al	110	3 mo	5 (4.7%)	105 (95.3%)	Cystotomy 1 Hematoma 2 Retention 6
Murphy et al	89	5 mo	0 (0%)	84 (94.4%)	Cystotomy 2
Hinoul et al	29	6 mo	2 (6.9%)	28 (96.5%)	Cystotomy 1
Withagen et al	43	6 mo	2 (4.7%)	35 (81.4%)	Rectal injury 1 Cystotomy 2 Retention 1
Groenen et al[1]	26	2 mo	1 (3.8%)	26 (100%)	Retention 5
Perscheler et al[1]	80	N/A	8 (10%) 5 (6.25%)	N/A	Hematoma 2 Cystotomy 2
Rivera et al[2]	82	3 mo	7 (11.7%)	N/A	Hematoma 1 Bleeding 1
Total	549	6 mo	34 (6.2%) 12 (2.6%)	81.4-100%	Rectal injury 1.7% Bleeding 1.3% Retention 6.7% Cystotomy 1.7%

* second figure is exposures requiring intervention

[1] All abstracts 2006 IUGA : *Int Urogynecol J* 2006;17(s.2):S212(abstracts)
[2] All abstracts 2006 AUGS : *Int Urogynecol J* 2006;17(S.3):S460(abstracts)

The references for the articles to support this monograph and its content were comprehensive, and this combination was more than adequate as a reference tool to surgeons doing transvaginal mesh POP surgery. There is no such document that I am aware of that provides this sort of helpful information for native tissue repairs. This information supplemented the information provided in the Prolift IFU. Also, to the extent the studies referenced in this report were co-authored by Ethicon personnel or sponsored by Ethicon, that constitutes another way in which Ethicon was making information regarding the safety and efficacy of the devices available to surgeons.

C. The patient brochures available for dissemination by physicians, as a supplement to a physician-specific discussion of the product with their patients, were never intended to

supplant the discussion by the doctor. Nevertheless, they provided adequate information to lay persons to supplement discussions with their physicians regarding POP surgery. The FDA public health notices, concerning surgical mesh, were included in my conversations with my patients in 2008. In 2011, the second notice was made available to the Ethicon surgeons as soon as it was published and was also included in my informed consent. The instructions and professional materials provided by Ethicon make it clear that their mesh products should be used by experienced physicians. The training and other educational opportunities provided by Ethicon allow surgeons to gain knowledge and experience regarding Ethicon's products. Ethicon was extremely thorough in their training of surgeons, and it was very important to Ethicon to have studies to support their recommendations and their products. These products had more studies and data evaluated than any of the other mesh companies that elicited my support. All of the other companies used Ethicon's data to compare their products, the majority of which I found unsatisfactory. Any of the complications that had been identified by the plaintiffs were studied and percentages discussed by Ethicon in professional education materials. Ethicon's goal with treating pelvic organ prolapse with a transvaginal mesh was based on sound study and success rates that far exceeded native tissue repairs, the need for recurrent operations for failures, and a desire to improve the quality of life for women with symptomatic pelvic organ prolapse.

VI. DESIGN DEFECTS

A. The clinical data demonstrates that the knitted, monofilament, lightweight, macroporous Prolene polypropylene mesh is biocompatible, has a minimal inflammatory response, and allows for adequate tissue growth, the mechanism by which mesh ultimately provides the necessary structural support in women with pelvic organ prolapse. This data also shows that Ethicon's mesh is not associated with significantly increased risks of infection over that of generally associated risk for vaginal surgery. There is no published data that suggests the mesh is cytotoxic or causes adverse inflammatory response, sarcoma, or cancer. By the sheer numbers of women in whom the mesh was implanted, if there was merit to a claim of cytotoxicity, you would certainly expect valid data to demonstrate that claim in replicable studies.

When the mesh is removed as an explant from patients, it is exposed to forces well beyond the intended force for a sling and prolapse procedure. Therefore, the change from an

explanted mesh is different than a host graft interaction because the act of explanting changes the mesh as it is removed from the patient. It has no predictive value. Prolene polypropylene has been used in millions of sutures, slings, and Gynemesh PS. A Medline search for sarcoma in polypropylene does not yield a single case of sarcoma or malignancy due to the use of polypropylene materials in humans. MSDS and rat studies reporting sarcoma formation after implantation of polypropylene discs and powder are not transferrable to humans.[82] The available data does not show any causal link between polypropylene and cancer.[83,84,85,86] There is no reliable evidence of human cytotoxicity. One cytotoxicity assessment of the TVT sling (made of Prolene polypropylene) in 1997 indicated the polypropylene may have cytotoxic potential;[87] however, this was not confirmed by the ISO Agarose diffuse method.[88] And the company correctly recognized that the assessment of the biocompatibility of the material had to take into consideration all available data, including clinical data, and when doing so, it was apparent that the Prolene materials did not have any clinically significant cytotoxicity translating to adverse patient outcomes.[89] Normal production of Prolene polypropylene has not shown any cytotoxicity at drug elution, ISO Agarose overlay method, or with extraction/filter paper method. All testing methods used monolayer of L-929 mouse fibroblast cells.[90,91] There are five decades of use of polypropylene mesh implants, and it is a stable, well-accepted biomaterial.[92] In recent years, there have been concerns regarding polypropylene degradation by high-magnification images that show meshes with "cracked" surfaces.[93] This referenced Clavé study; there were many

[82] King AB, Goldman HB. Current controversies regarding oncologic risk associated with polypropylene midurethral slings. Curr Urol Rep. 2014 Nov;15(11):453.
[83] Moalli P, et al., Polypropylene mesh: evidence for lack of carcinogenicity. Int Urogynecol J. 2014 May;25(5):573-6.
[84] March 12, 2014, *AUGS SUFU Frequently Asked Questions*.
[85] King AB, et al. Is there an association between polypropylene midurethral slings and malignancy? Urology. 2014 Oct;84(4):789-92.
[86] Linder BJ, et al., Evaluation of the local carcinogenic potential of mesh used in the treatment of female stress urinary incontinence. Int Urogynecol J. 2016 Sep;27(9):1333-6.
[87] ETH.MESH.08476311.
[88] Eth.mesh.08476314.
[89] C. Linsky memo re Cytotoxicity Risk Assessment for the TVT (Ulmsten) Device, ETH.MESH.00349228.
[90] ETH.MESH.08476315.
[91] ETH.MESH.08476316.
[92] AUGS/SUFU Facts by Providers, *Urogynecology* (March 2010).
[93] Clavé A, et al., Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J 2010;21:261-270.

methodological flaws. While these purported surface changes were hypothesized to lead to adverse clinical outcomes, they cannot be confirmed, and there is no extensive peer review literature that supports this hypothesis. There are studies that suggest clinically significant mesh degradation occurs, but there are other studies that indicate that the surface cracking interpreted by some as being evidence of mesh degradation is actually cracking in a biofilm overlying the polypropylene.[94] Based on my positive experience using the mesh products in my patients and on my reading of the published literature, it is my opinion that clinically significant mesh degradation does not occur with Ethicon's products. The large volume of medical literature, which includes over 100 Gynemesh PS studies, metaanalysis, and systematic reviews, do not support that the mesh is cytotoxic, that it degrades, or leads to harmful inflammatory responses in humans. Actually, the use of macroporous type 1 Prolene polypropylene has been shown to be the most biocompatible material for the use and treatment of POP with high-level clinical data. Overall, the data shows that Gynemesh PS, Prolift, Prolift+M, and Prosima are safe and effective. They are not defective, and these incredibly studied devices are quite useful in the approach to repairing and resolving pelvic organ prolapse.

Mesh shrinkage or contraction is discussed in the literature, but is somewhat of a misnomer. Scar tissue does shrink or contract during the healing process, and the scar tissue that is incorporated into the Gynecare pelvic organ prolapse products is no exception, but the mesh itself does not contract or shrink. Scar tissue that forms following native tissue repairs or implantation of biologic graft materials also shrinks and contracts.

Finally, it is my opinion that the data does not support the theories that mesh is cytotoxic, that it degrades or causes harmful inflammatory response, that the pore size, weight, and other features are harmful or cause significant detrimental clinical outcomes. The pore size of the products is far in excess of the 75-micron threshold widely recognized to constitute a macroporous mesh, and allows for excellent tissue ingrowth and very low rates of infection. While there is no agreed-upon classification system for the weight or density of meshes, the Gynemesh PS and Ultrapro mesh used in the products addressed in this report is lightweight mesh. Ethicon studied these products more than any other company in this surgical arena

[94] Ong KL, et al., The Myth: In Vivo Degradation of Polypropylene Meshes. IUGA 2016, Abs. PP 19; de Tayrac R and Letouzey V, Basic science and clinical aspects of mesh infection in pelvic floor reconstructive surgery. Int Urogynecol J 2011 Jul;22(7):775-80.

and more than adequately trained the physicians that performed the surgery. Ethicon also kept these physicians well informed of all the data as it was collected, both supportive and critical.

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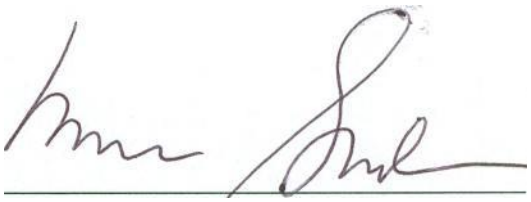

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